Cavagnero *et al.* and Lappi *et al.* The Examiner further rejected claims 1-17 under 35 U.S.C. § 102, first paragraph for failure of written description. In addition, claims 6-8, 11-13 and 15 were rejected under 35 U.S.C. § 102, first paragraph for lack of enablement. Applicant has amended claim 1, has added claims 24-102, and has canceled claims 3-23. Applicant respectfully submits that amended claim 1 and newly added claims 24-102 are fully supported by the specification and that no new matter is added through this amendment and the introduction of these new claims. Below we address each of the rejections stated in the Office Action as if it were applied to the amended and newly added claims.

Amendment and Addition of Claims

Claim 1 has been amended, claims 3-23 have been canceled and new claims 24-102 have been added. Claim 2 remains unchanged. Support for the new claims can be found in the claims as originally filed and throughout the specification. Specifically, claim 1 has been amended to recite that the chimeric peptides of the invention comprise an N-terminal opioid receptor binding moiety and a C-terminal Substance P (SP) receptor agonist binding moiety. Support for such language can be found on page 17 lines 9-13 and Figures 1 and 2 in the teaching that the working examples ESP6 and ESP7 were constructed so that the opioid receptor binding moiety (*e.g.*, endomorphin 2) is at the amino terminus and the SP receptor binding moiety is at the carboxy terminus of the chimeric peptide. In addition, with respect to the agonist nature of the SP receptor binding moiety, support can be found in the Examples and in Figure 9 in the teaching that testing for binding of the chimeric peptide ESP7 to SP receptors involved antagonizing the SP portion of the peptide with an appropriate antagonist (*e.g.* RP67580). See: page 23 lines 18-

21 and page 25 lines 10-18 in the specification. One of ordinary skill in the art would appreciate that the SP receptor binding moiety of the chimeric peptides of the invention is thus understood to be agonist. Claims 24 and 25 were added to recite that the opioid receptor binding moiety may comprise a ligand, and that it binds to at least one opioid receptor selected from the μ, δ and κ receptors (*e.g.*, the opioid receptor binding moiety may exhibit different selectivities for each of these receptors). Support for this subject matter can be found *inter alia* in original claim 3 and, for example, in Tables 1-3 and on page 13 lines 11-18, page 14 lines 3-13 and page 15 lines 3-12 of the specification. Claim 26 recites that the opioid receptor binding moiety is agonist, which finds support in Tables 1-3 and on page 13 line 11, page 14 line 3 and page 15 line 4 of the specification. Claims 27-33 find support in original claims 4 and 9, on page 13 lines 10-18 of the specification and in Table 1. Support for claims 34-38 can be found in original claim 9, on page 14 lines 2-13 of the specification and in Table 2. Claims 39-44 find support in original claim 9, on page 15 lines 2-12 of the specification and in Table 3. Support for claims 45-56 can be found in original claim 10, on page 16 lines 1-11 of the specification and in Table 4. Claim 57 finds support *inter alia* in original claim 15. Support for claims 58 and 59 can be found on page 17 lines 9-13 and in Figures 1 and 2. Claims 60 and 61 find support in original claim 14 and throughout Tables 1-4 in the teaching that several of the recited opioid and SP receptor ligands comprise one or more D-amino acids. Finally, support for claims 62-102 can be found *inter alia* in original claims 16 and 17.

Each of the objections discussed in the Examiner's Office Action is addressed below as if it were applied to amended claim 1 and newly added claims 24-102, to expedite prosecution of the present application.

Applicant respectfully submits that amendment and addition of the claims, as described above and detailed herein, does not present new matter, and Applicant thus respectfully requests entry of these additions, and consideration of these additions in the following remarks.

Rejection of claims 6-8, 11-13 and 15 under 35 U.S.C. § 112, first paragraph - enablement

Claims 6-8, 11-13 and 15 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention. Specifically, the Examiner argues that the specification provides no guidance or working example of how to make functional chimeras comprising ***derivatives*** or ***fragments*** of the recited binding moieties, including those comprising ***D-amino acids***, or a ***plurality*** of binding moieties. The Examiner further states that these factors, along with the lack of predictability to one of ordinary skill in the art to make these derivatives and fragments leads to the conclusion that undue experimentation is necessary to practice the invention as claimed.

Claims 6-8 and 11-13 and 15 have been canceled, thereby obviating the rejection. Applicant would like to point out, however, that the language objected to by the Examiner (*e.g.*, "derivatives", "fragments" and "D-amino acids") is used in the newly added claims and thus the appropriateness of this language with respect to the enablement issue will be addressed. Specifically, claims 25, 31-33, 38, 43-45, 54-57 and 61 (as well as the corresponding composition claims) recite the language said to lack enablement and thus the rejection for lack of

enablement under 35 U.S.C. § 112, first paragraph will be addressed as if it were applied to these newly added claims.

The standard for enablement is based on the determination of whether the disclosure contains sufficient information regarding the subject matter of the claim as to enable one skilled in the art to make and use the claimed invention. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied (*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); MPEP 2164.01(b)). Applicant is not required to disclose every operable species, but only representative examples, with enough teaching and guidance so as to enable a person of ordinary skill in the art to practice the invention without undue experimentation.

Applicant respectfully disagrees that the specification does not reasonably provide enablement commensurate with the scope of these claims, and instead submits that the specification provides sufficient guidance for one of ordinary skill in the art to make and use the invention as claimed without undue experimentation. Specifically, Applicant respectfully submits that the specification ***does*** provide sufficient guidance and ***does*** teach one of ordinary skill in the art how to make functional chimeric peptides comprising an N-terminal opioid receptor binding moiety and a C-terminal Substance P (SP) receptor agonist binding moiety, without undue experimentation.

The specification teaches that the opioid receptor binding moiety should preferably be N-terminal and that it should preferably end with a Tyrosine residue, most preferably a free Tyrosine residue (see, for example, Tables 1-3 on pages 14-15 and Figures 1 and 2). With

respect to the SP receptor binding moiety, the specification teaches that it should preferably be C-terminal, and that its terminal –COOH moiety should preferably be protected (see, for example, Table 4 on pages 16-17 and Figures 1 and 2). The specification provides examples of starting materials or precursors suitable to construct the chimeric peptides of the invention (see, for example Table 1-4 on pages 14-17 of the Specification), and also provides ample teaching of potential methods suitable to prepare N-terminal derivatives or fragments, and C-terminal derivatives or fragments of the recited opioid and SP receptor binding moieties, respectively. For example, in the section entitled "Production of derivatives and analogs" found on pages 9-13 of the specification, it is recited (page 9 lines 26-28) that "variants of the peptides that function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants of the parent peptide for peptide agonist or antagonist activity". The Specification also states: "Derivatives, fragments and analogs provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively. Fragments are, at most, one nucleic acid-less or one amino acid-less than the wild type full length sequence. Derivatives and analogs may be full length or other than full length, if said derivative or analog contains a modified nucleic acid or amino acid, as described *infra*." (See the paragraph bridging page 10 and page 11 in the Specification). The specification further recites various methods, known in the art, for preparing derivatives and analogs of the inventive chimeric peptides, citing several references (pages 9-13 of the Specification).

In addition, the specification provides sufficient teaching and guidance to enable one of ordinary skill in the art to prepare opioid or SP receptor binding moieties comprising at least one D-amino acid, to make the chimeric peptides of the invention. For example, lines 20-27 on page 5 of the Specification recite that "chemical synthesis of peptides facilitates the incorporation of modified or unnatural amino acids, including D-amino acids and other small organic molecules. Replacement of one or more L-amino acids in a peptide with the corresponding D-amino acid isoforms can be used to increase the resistance of peptides to enzymatic hydrolysis, and to enhance one or more properties of biologically active peptides, *i.e.*, receptor binding, functional potency or duration of action", citing several references. Furthermore, examples of D-amino acid-containing opioid and SP receptor binding moieties are provided in Tables 1-4 on pages 14-17 of the Specification. One skilled in the art would recognize that most endogenous opiates have a glycine residue (devoid of chirality) at the 2-position of the peptide chain (next to the Tyrosine residue), and would thus appreciate that where opioid receptor binding moieties comprise a D-amino acid, the D –amino acid is preferably inserted at the 2-position of the peptide chain, as illustrated by SEQ ID Nos.: 4, 10 and 12-17.

In addition, Applicant submits that the state of the art in the area of opioid peptides and tachykinin peptides is quite high. The same is true for the field of peptide synthesis, as illustrated by the citations listed on page 5 lines 5-19 of the Specification. One of ordinary skill in this art would be expected to have at least an advanced degree, such as a Ph.D. Applicant asserts that such a person armed with knowledge in the cited scientific references and Applicant's teachings could make the claimed chimeric peptides without undue experimentation.

Therefore Applicant submits that the claims are indeed enabled and requests that the rejection for lack of enablement be withdrawn.

Rejection of claims 1-17 under 35 U.S.C. § 112, first paragraph – written description

Claims 1-17 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner argues that the specification and claims fail to indicate the distinguishing attributes shared by the members of the genus, and because the genus is highly variant, "opioid and nociceptive binding moiety" alone is insufficient to describe the genus.

Claims 3-17 have been canceled, and claim 1 has been amended to recite that the chimeric peptides of the invention comprise an N-terminal opioid receptor binding moiety and a C-terminal Substance P receptor agonist binding moiety, thereby obviating the rejection. Applicant submits that the invention recited in the amended and newly added claims was clearly described in the application as filed. Specifically, the specification states: "In one embodiment, the novel chimeric peptide is ESP7, SEQ ID No:42 (FIG. 1). Because it includes endomorphin-2 at the N-terminus and SP (7-11) at the C-terminus, ESP7 is designed to bind to the μ receptor and the NK1 receptor." Thus, the specification teaches that the opioid receptor binding moiety should preferably be N-terminal and that the SP receptor binding moiety should preferably be C-terminal. The specification also provides teaching that the opioid receptor binding moiety should preferably end with a Tyrosine residue, most preferably a free Tyrosine residue, and that the SP

receptor binding moiety should preferably have a protected terminal –COOH moiety. Examples of opioid and SP receptor binding ligands satisfying these characteristics are described in Tables 1-4 on pages 14-17 of the Specification and in Figures 1 and 2.

In view of the foregoing arguments, Applicant respectfully submits that, as required under 35 U.C.C. § 112, first paragraph, the disclosure conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed, and thus respectfully requests that the rejection under 35 U.C.C. § 112, first paragraph (written description) be withdrawn.

Rejection of claims 1-17 under 35 U.S.C. § 103 (a) over Kream et al. (U.S. Patent No. 5,891,842; "Kream"), Cavagnero et al. (Life Sci., 49:495-503, 1991; "Cavagnero"), and Lappi et al. (U.S. Patent No. 6,063,758; "Lappi")

Claims 1-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kream in view of Cavagnero and further in view of Lappi. Claim 1 has been amended, claims 3-23 have been canceled and new claims 24-102 have been added, thereby rendering the rejection under 35 U.S.C. §103(a) moot. However, in an effort to expedite prosecution, the rejection will be addressed as if it were applied to amended claim 1 and newly added claims 24-102.

The legal standard for establishing a prima facie case of obviousness requires that the following three criteria be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable

expectation of success; and (3) the prior art reference(s) must teach or suggest all the claimed limitations.

Applicant respectfully disagrees that the claimed invention is obvious over the combination of the cited references, and further submits that the Examiner has applied an improper "obvious to try" rationale to support the stated rejection. Specifically, Applicant submits that claims 1-2 and 24-102 are not obvious over Kream, Cavagnero and Lappi.

The Examiner states that Kream teaches that concurrent administration of marginal doses of opioids, including those that act at the μ opioid receptor, in combination with marginal doses of a nociceptive ligand, Substance P (SP) produces a powerful potentiation and enhancement of an opioid response in animals when administered as pharmaceutical compositions in vivo. However, the Examiner has conceded that Kream does not teach using these binding moieties as chimeric peptides. In fact, Kream invokes the concurrent use of ***at least two*** distinct pharmacological entities for inducing analgesia, as it is emphasized throughout the patent. Specifically, Kream's invention involves co-administration of an opiate with Substance P as ***separate*** compounds as a means to activate both opioid and SP receptors for enhanced analgesia. Kream provides no teaching or suggestion of combining an opioid receptor binding moiety with a Substance P agonist binding moiety within a single chemical entity.

The Examiner asserts that Cavagnero teaches that opioid peptide chimeras can be prepared to produce analogs with specific characteristics, and that these compounds bind to and activate opioid receptors in binding and functional assays. However the Examiner has conceded that Cavagnero does not teach SP chimeras. In addition, Applicant submits that Cavagnero is

only concerned with chimeras acting at different receptors subtypes ***within the same receptor class*** (namely the μ and δ opioid receptors). There is no teaching or suggestion in Cavagnero to design a peptide that would simultaneously bind to two ***different receptors***. Specifically, there is no indication or teaching in Cavagnero to combine an N-terminal opioid receptor binding moiety with a C-terminal SP receptor binding moiety within the same peptide.

The Examiner asserts that Lappi teaches SP, and analogs thereof, conjugated to Saporin, as well as pharmaceutical compositions for the treatment of pain perception in a subject. Applicant submits that Lappi's invention differs from that of Applicant in that it teaches the conjugation of an NK-1 binding moiety with a ribosome-inactivating protein, thereby producing cytotoxins that are specific for NK-1 receptor-bearing cells (see column 11 lines 37-50). The SP receptor binding moiety binds to the NK-1 receptor on the cell; the conjugate is then internalized, and Saporin inactivates the neuronal protein synthesis mechanism, which results in neuronal cell death and may decrease pain perception. There is no teaching or suggestion in Lappi to design a peptide that would simultaneously bind to two different receptors. Specifically, there is no teaching or suggestion in Lappi to combine an opioid receptor binding moiety with an SP receptor binding moiety, more specifically an N-terminal opioid receptor binding moiety with a C-terminal SP receptor binding moiety within the same peptide, and that this combination may enhance analgesia.

Accordingly, Applicant respectfully submits that a person of ordinary skill in the art would ***not*** have found "obvious to try" to combine the teachings of Kream, Cavagnero and Lappi, because there was no suggestion to combine the references, nor was there any reasonable expectation of success in the combination in order to achieve the claimed invention.

Specifically, there is no reasonable expectation of success that a chimeric peptide comprising an N-terminal opioid receptor binding moiety and a C-terminal SP agonist binding moiety would bind to both the opioid and SP receptors, and induce analgesia. Applicant would like to point out that the teaching or suggestion to make the claimed combination and the reasonable expectation of success ***must both be found in the prior art*** and ***cannot*** be based on Applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed, Cir, 1991); MPEP 706.02(j)). In addition, Applicant submits that the claims as amended in the present response are not obvious over the combination of the cited references because the combination does not teach all of the claim limitations (*e.g.*, (1) a chimeric peptide comprising (2) an N-terminal opioid receptor binding moiety and (3) a C-terminal SP agonist binding moiety).

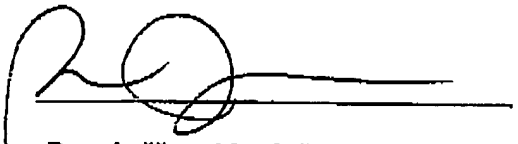
Since there is no suggestion or motivation to combine the teachings of Kream, Cavagnero and Lappi and there is no reasonable expectation of success in the combination to achieve the claimed invention, and since the references do not teach all of the claim limitations, the claims as set forth in the present response cannot be obvious over Kream, in view of Cavagnero and further in view of Lappi.

Conclusion

In view of the foregoing Amendment and Remarks, Applicant respectfully submits that the present case is now in condition for allowance; a Notice to that effect is hereby requested. Applicant would like to thank the Examiner for his careful review and consideration of this case and if the Examiner believes that a telephone interview would be of assistance in advancing the prosecution of this application, the Examiner is invited to telephone the undersigned (617) 248-5175.

Although it is believed that there is no fee associated with this Response, if Applicant is mistaken, please charge any fees to our Deposit Account No.: 03-1721.

Respectfully submitted,



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Appendix
Version with Markings to Show Changes Made

1. (Amended) A chimeric peptide comprising an N-terminal opioid receptor binding moiety and a [nociceptive] C-terminal Substance P receptor agonist binding moiety.

2. (Unchanged) The peptide of claim 1, wherein said peptide induces analgesia when administered to a mammal.

24. (Newly added) The peptide of claim 1 wherein said opioid receptor binding moiety binds to at least one opioid receptor selected from the group consisting of the μ receptor, the δ receptor and the κ receptor.

25. (Newly added) The peptide of claim 24 wherein said opioid receptor binding moiety comprises a ligand, N-terminal fragment or N-terminal derivative thereof, which ligand binds to at least one opioid receptor selected from the group consisting of the μ receptor, the δ receptor and the κ receptor.

26. (Newly added) The peptide of claim 1, 24 or 25 wherein said opioid receptor binding moiety is an opioid receptor agonist.

27. (Newly added) The peptide of claim 1, 24 or 25 wherein said opioid receptor binding moiety selectively binds the μ receptor.

28. (Newly added) The peptide of claim 27 wherein said opioid receptor binding moiety is a μ receptor agonist.

29. (Newly added) The peptide of claim 28 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.

30. (Newly added) The peptide of claim 29 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.

31. (Newly added) The peptide of claim 30 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 1-11, N-terminal fragments and N-terminal derivatives thereof.

32. (Newly added) The peptide of claim 30 wherein said opioid receptor binding moiety is endomorphin 1, endomorphin 2, an N-terminal fragment or N-terminal derivative thereof.

33. (Newly added) The peptide of claim 32 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 2-3, N-terminal fragments and N-terminal derivatives thereof.

34. (Newly added) The peptide of claim 1, 24 or 25 wherein said opioid receptor binding moiety selectively binds the δ receptor.

35. (Newly added) The peptide of claim 34 wherein said opioid receptor binding moiety is a δ receptor agonist.

36. (Newly added) The peptide of claim 35 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.

37. (Newly added) The peptide of claim 36 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.

38. (Newly added) The peptide of claim 37 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 12-17, N-terminal fragments and N-terminal derivatives thereof.

39. (Newly added) The peptide of claim 1, 24 or 25 wherein said opioid receptor binding moiety selectively binds the κ receptor.

40. (Newly added) The peptide of claim 39 wherein said opioid receptor binding moiety is a κ receptor agonist.

41. (Newly added) The peptide of claim 40 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.

42. (Newly added) The peptide of claim 41 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.

43. (Newly added) The peptide of claim 42 wherein said opioid receptor binding moiety is a dynorphin peptide, N-terminal fragment or N-terminal derivative thereof.

44. (Newly added) The peptide of claim 43 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 18-20 and 44, N-terminal fragments and N-terminal derivatives thereof.

45. (Newly added) The peptide of claim 1, 24 or 25 wherein said Substance P receptor agonist binding moiety comprises Substance P, a C-terminal Substance P fragment or a C-terminal Substance P derivative.

46. (Newly added) The peptide of claim 1, 24 or 25 wherein the –COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is protected.

47. (Newly added) The peptide of claim 46 wherein the –COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is amidated.

48. (Newly added) The peptide of claim 47 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Met-NH_2.

49. (Newly added) The peptide of claim 48 wherein said Substance P receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 21, 36 and 38-41, N-terminal fragments and N-terminal derivatives thereof.

50. (Newly added) The peptide of claim 46 wherein the -COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is esterified.

51. (Newly added) The peptide of claim 50 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is a methyl ester.

52. (Newly added) The peptide of claim 51 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-OMe, Lys-COOMe or Arg-COOMe.

53. (Newly added) The peptide of claim 52 wherein said Substance P receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 25-27, N-terminal fragments and N-terminal derivatives thereof.

54. (Newly added) The peptide of claim 50 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is an ethyl ester.

55. (Newly added) The peptide of claim 54 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-COOEt, Lys-COOEt or Arg-COOEt.

56. (Newly added) The peptide of claim 55 wherein said Substance P receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 28-30, N-terminal fragments and N-terminal derivatives thereof.

57. (Newly added) The peptide of claim 1 wherein the opioid receptor binding moiety is selected from the group consisting of endomorphin 1, endomorphin 2, N-terminal fragments and N-terminal derivatives thereof; and the Substance P receptor binding moiety is selected from the group consisting of Substance P, C-terminal fragments and C-terminal derivatives thereof.

58. (Newly added) The chimeric peptide of claim 1 wherein the peptide has SEQ ID No: 42.

59. (Newly added) The chimeric peptide of claim 1 wherein the peptide has SEQ ID No: 43.

60. (Newly added) The peptide of claim 1, wherein said peptide comprises at least one non-natural amino acid.

61. (Newly added) The peptide of claim 60 wherein said peptide comprises at least one D-amino acid.

62. (Newly added) A pharmaceutical composition comprising the peptide of claim 1 and a pharmaceutically acceptable diluent.

63. (Newly added) The pharmaceutical composition of claim 62, further comprising an adjuvant.

64. (Newly added) The composition of claim 62, wherein said peptide induces analgesia when administered to a mammal.

65. (Newly added) The composition of claim 62 wherein said opioid receptor binding moiety binds to at least one opioid receptor selected from the group consisting of the μ receptor, the δ receptor and the κ receptor.

66. (Newly added) The composition of claim 62 wherein said opioid receptor binding moiety comprises a ligand, N-terminal fragment or N-terminal derivative thereof, which ligand binds to at least one opioid receptor selected from the group consisting of the μ receptor, the δ receptor and the κ receptor.

67. (Newly added) The composition of claim 62, 65 or 66 wherein said opioid receptor binding moiety is an opioid receptor agonist.

68. (Newly added) The composition of claim 62, 65 or 66 wherein said opioid receptor binding moiety selectively binds the μ receptor.

69. (Newly added) The composition of claim 68 wherein said opioid receptor binding moiety is a μ receptor agonist.

70. (Newly added) The composition of claim 69 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.

71. (Newly added) The composition of claim 70 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.

72. (Newly added) The composition of claim 71 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 1-11, N-terminal fragments and N-terminal derivatives thereof.

73. (Newly added) The composition of claim 71 wherein said opioid receptor binding moiety is endomorphin 1, endomorphin 2, an N-terminal fragment or N-terminal derivative thereof.

74. (Newly added) The composition of claim 73 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 2-3, N-terminal fragments and N-terminal derivatives thereof.

75. (Newly added) The composition of claim 62, 65 or 66 wherein said opioid receptor binding moiety selectively binds the δ receptor.

76. (Newly added) The composition of claim 75 wherein said opioid receptor binding moiety is a δ receptor agonist.

77. (Newly added) The composition of claim 76 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.

78. (Newly added) The composition of claim 77 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.

79. (Newly added) The composition of claim 78 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 12-17, N-terminal fragments and N-terminal derivatives thereof.

80. (Newly added) The composition of claim 62, 65 or 66 wherein said opioid receptor binding moiety selectively binds the κ receptor.

81. (Newly added) The composition of claim 80 wherein said opioid receptor binding moiety is a κ receptor agonist.

82. (Newly added) The composition of claim 81 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is a free amine.

83. (Newly added) The composition of claim 82 wherein the N-terminal amino acid residue of said opioid receptor binding moiety is Tyr.

84. (Newly added) The composition of claim 83 wherein said opioid receptor binding moiety is a dynorphin peptide, N-terminal fragment or N-terminal derivative thereof.

85. (Newly added) The composition of claim 84 wherein said opioid receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 18-20 and 44, N-terminal fragments and N-terminal derivatives thereof.

86. (Newly added) The composition of claim 62, 65 or 66 wherein said Substance P receptor agonist binding moiety comprises Substance P, a C-terminal Substance P fragment or a C-terminal Substance P derivative.

87. (Newly added) The composition of claim 62, 65 or 66 wherein the –COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is protected.

88. (Newly added) The composition of claim 87 wherein the –COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is amidated.

89. (Newly added) The composition of claim 88 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Met-NH_2.

90. (Newly added) The composition of claim 89 wherein said Substance P receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 21, 36 and 38-41, N-terminal fragments and N-terminal derivatives thereof.

91. (Newly added) The composition of claim 87 wherein the –COOH moiety of the C-terminal amino acid residue of said Substance P receptor binding moiety is esterified.

92. (Newly added) The composition of claim 91 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is a methyl ester.

93. (Newly added) The composition of claim 92 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-OMe, Lys-COOMe or Arg-COOMe.

94. (Newly added) The composition of claim 93 wherein said Substance P receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 25-27, N-terminal fragments and N-terminal derivatives thereof.

95. (Newly added) The composition of claim 91 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is an ethyl ester.

96. (Newly added) The composition of claim 95 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-COOEt, Lys-COOEt or Arg-COOEt.

97. (Newly added) The composition of claim 96 wherein said Substance P receptor binding moiety is selected from the group consisting of peptides having SEQ ID Nos: 28-30, N-terminal fragments and N-terminal derivatives thereof.

98. (Newly added) The composition of claim 62 wherein the opioid receptor binding moiety is selected from the group consisting of endomorphin 1, endomorphin 2, N-terminal fragments and N-terminal derivatives thereof; and the Substance P receptor binding moiety is selected from the group consisting of Substance P, C-terminal fragments and C-terminal derivatives thereof.

99. (Newly added) The composition of claim 62 wherein the peptide has SEQ ID No: 42.

100. (Newly added) The composition of claim 62 wherein the peptide has SEQ ID No: 43.

101. (Newly added) The composition of claim 62, wherein said peptide comprises at least one non-natural amino acid.

102. (Newly added) The composition of claim 101 wherein said peptide comprises at least one D-amino acid.